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(57) Abstract

Binary pharmaceutical formulations comprising (i) a cyclosporine compound, (ii) a lipophilic phase and (iii) a surfactant provide bioavailability of the active ingredient which is equivalent to that provided by ternary compositions, but without the need for a hydrophilic phase.

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# LIPOPHILIC BINARY SYSTEMS FOR THE ADMINISTRATION OF LIPOPHILIC COMPOUNDS

## Technical Field

The present invention relates to pharmaceutical compositions containing lipophilic medicinal compounds, suitable for oral as well as topical, local and other routes of administration. In particular, the invention relates to binary formulations of cyclosporines which comprise a lipophilic phase and one or more surfactants, but which lack a hydrophilic phase.

## Background of the Invention

Pharmaceutical compounds which are highly lipophilic present considerable formulation challenges. Because of their low solubility in aqueous media, including the contents of the mammalian digestive tract, they often suffer from poor or variable bioavailability when given orally or via other routes that require transmembrane absorption. Examples of such medicinal compounds include the immunosuppressants cyclosporine and FK506 (tacrolimus); protease inhibitors such as ritonavir; central nervous system drugs such as tiagabine; and anti-inflammatory agents such as zileuton and other 5-lipoxygenase inhibitors.

One method of formulating lipophilic compounds is to combine them with glyceride carriers which form emulsions upon mixing with water. Emulsions are described, for example, in U.S. Patent No. 4,388,307 issued to Cavanak, a commercial example of which is the cyclosporine-containing product SANDIMMUNE® oral solution. This product comprises the emulsifier LABRAFIL® (a polyoxyethylated kernel oil), olive oil and alcohol, with the compound cyclosporin A present at a concentration of 100 mg/ml. Cavanak suggests that such glyceride carriers may assist in alleviating problems of physical instability such as precipitation of the drug from solution, and may also enable higher plasma concentrations.

More recently, it has been proposed that a preferred vehicle for lipophilic compounds is the so-called "self-emulsifying drug delivery system" which, when exposed to an aqueous medium, forms a fine oil-in-water emulsion with little or no agitation. The property of self-emulsification permits such formulations to be administered in concentrated form, as for example in a hard gelatin or soft elastic capsule, with the expectation that a fine emulsion will be formed in the digestive tract. Moreover, it has been suggested that self-emulsifying formulations, when given orally, may offer improvements in both the rate and extent of absorption of the medicinal compound and can result in reduced variability in plasma concentration profiles. (*See*, S. A. Charman *et al.*, Pharmaceutical Research 9(1):87-93 (1992), and N. H. Shah *et al.*, International Journal of Pharmaceutics 106:15-23 (1994).) Additionally, emulsions which have been prepared by combining a self-emulsifying

pre-concentrate with an aqueous medium appear to benefit, due to their small droplet diameter, from improved physical stability when compared with conventional emulsions.

Previously-disclosed self-emulsifying systems include those in which a lipophilic drug is combined with mixtures of (i) medium-chain triglycerides and nonionic surfactants, (ii) vegetable oils and partial glycerides such as polyglycolyzed glycerides or medium-chain mono- and diglycerides, or (iii) vegetable oils and nonionic surfactants such as polysorbate 80 or PEG-25 glyceryl trioleate. Other formulations have been characterized as self-emulsifying, including the above-mentioned SANDIMMUNE® cyclosporine formulation; however, these additionally contain a substantial amount of a solubilizing agent or solvent such as ethanol, rendering them unsuitable for certain uses such as filling into gelatin capsules, from which the solvent can readily escape.

Self-emulsifying formulations which seek to overcome this drawback are disclosed by Hauer *et al.* in U.S. Patent No. 5,342,625. In these formulations, a "microemulsion pre-concentrate" of a cyclosporine is formed by combining the drug with (I) a hydrophilic phase, (II) a lipophilic phase, and (III) a surfactant, as well as optional thickeners, anti-oxidants or other excipients. Unfortunately, the complexity of these ternary formulations may make them costly and difficult to manufacture.

There exists, consequently, a need for formulations of lipophilic drugs such as cyclosporines that are simpler and easier to prepare than the ternary systems described above. Kurihara *et al.*, in U.S. Patent No. 4,990,337, propose cyclosporine-containing formulations that comprise medium-chain, $C_6$-to-$C_{10}$, mono- and diglycerides. However, additional formulations are sought which offer an advantageous combination of physical stability, desirable pharmacokinetics and/or ease of manufacture.

## Summary of the Invention

Surprisingly, it has now been found that many of the problems associated with the administration of lipophilic compounds such as cyclosporines may be overcome by the use of a simple binary system of excipients comprising only a lipophilic phase and a surfactant (or mixture of surfactants). In particular, the invention provides pharmaceutical compositions containing a cyclosporine compound in combination with a lipophilic phase and a surfactant, but not containing hydrophilic solvents. Such binary formulations are novel; moreover, the cyclosporine-containing formulations of the present invention are stable, simple to prepare, and commercially attractive by virtue of their pharmacokinetic properties.

As used herein, the terms "binary system", "binary composition" and "binary system of excipients" include those formulations and compositions which contain, in addition to the active ingredient or ingredients, a combination of at least one lipophilic solvent and at least one

surfactant in the absence of any hydrophilic solvents or excipients (such as water). For example, freeze-dried formulations that contain even a minimal amount of water are not considered to be binary compositions as that term is used herein.

To prepare the pharmaceutical compositions of the invention, a binary system of the invention is combined with a lipophilic active ingredient, such as a cyclosporine compound. The term "cyclosporine" as used herein refers to one or more of the cyclosporines, and especially to cyclosporin A, as described in United States Patent No. 4,117,118 issued to Härri *et al.* and incorporated herein by reference.

If desired, binary compositions of the present invention may be selected which are bioequivalent to compositions that use the ternary excipient systems of the prior art; that is, when such binary and ternary compositions containing equal amounts of active ingredient are administered separately to comparable test subjects, about the same amount of active ingredient will be delivered to the subjects' bloodstreams by the inventive composition as by the ternary composition. The amount of drug delivered (or other pharmacokinetic property) may be measured by any of the methods known in the art, as for example the maximum plasma concentration ($C_{max}$), the time from dosing until the maximum plasma concentration is reached ($T_{max}$), and the integral or time-course of plasma concentration over time (area under the curve, or AUC).

As described earlier, the binary systems of the invention comprise a lipophilic phase and one or more surfactants. Unless otherwise specified, the term "lipophilic component" or "lipophilic solvent" refers to a pharmaceutically acceptable solvent, carrier, excipient, or diluent that has an affinity for fats or lipids. The term "lipophilic phase" refers to the portion of the composition that is lipophilic, which phase can be a single component or a mixture of components.

The term "surfactant" as used herein describes that portion of a composition of the invention which comprises one or more surfactants. The surfactants may be any of the known pharmaceutically acceptable surfactants, including nonionic, anionic and cationic surfactants. A single surfactant or a mixture of surfactants may be used.

Unless otherwise specified, all percentages are weight percentages based on the total weight of the pharmaceutical composition.

Detailed Description of the Invention

In binary compositions according to the present invention, the lipophilic phase may comprise one or more of any of the known pharmaceutically acceptable lipophilic solvents or excipients that are capable of dissolving a cyclosporine compound. Suitable classes of lipophilic solvents include, for example, fatty acid esters of glycerol; fatty acid esters of propylene glycol; vegetable oils; mineral oils; and acetylated mono- and diglycerides. Preferred solvents include fatty acid esters of propylene glycol as well as $C_{12}$ and longer fatty acid esters of glycerol .

Particular lipophilic phase components useful in the compositions of the invention include, but are not limited to, propylene glycol mono- and/or dicaprylate/caprates; propylene glycol mono- and/or dilaurate (for example, LAUROGLYCOL®, available from Gattefossé Corporation, Westwood, New Jersey); vegetable oil; corn oil; sesame oil; safflower oil; peanut oil; olive oil; cottonseed oil; glyceryl monostearate; glyceryl caprylate/caprate (for example, CAPMUL® MCM, available from Abitec Corporation, Columbus, Ohio); glyceryl mono-, di- and/or trioleate (for example, CAPMUL® GMO, available from Abitec Corporation), or PECEOL®, available from Gattefossé); caprylic/capric triglyceride (for example, NEOBEE® M-5, available from Stepan Corporation); and fractionated coconut oils, such as the MIGLYOL® 810, 812 and 818 products, available from Huls, Ltd. (Wolverton Mill S., UK). Of these, glyceryl caprylate/caprate, for example, CAPMUL® MCM is preferred.

The lipophilic phase, comprising one or more lipophilic solvents, generally comprises about 10 to 90% by weight of the pharmaceutical composition. The precise proportion will vary depending on the nature of the lipophilic solvent(s) used, the amount of active ingredient present, the dosage type, and other factors known to those of skill in the art. Preferably the lipophilic phase comprises about 20 to 85% by weight, and more preferably about 40 to 60% by weight of the pharmaceutical composition of the invention.

The binary systems of the present invention also comprise at least one surfactant in combination with the above lipophilic phase. While not intending to be bound by theory, the surfactant is believed to assist in the formation of a micellar system or a microsuspension upon contact with an aqueous medium such as gastrointestinal fluids in a way that the solubility of the active ingredient is enhanced. The size of the particles present in this micellar or microsuspension system are in the sub-micron (sub-micrometer) range and can vary over time. Any of the known pharmaceutically acceptable surfactants may be used, including nonionic, anionic, cationic, and combinations thereof. Of these, nonionic surfactants are preferred; especially preferred are (i) surfactants having a hydrophile/lipophile balance (HLB) of 10 or more or (ii) mixtures of surfactants which, when combined, exhibit a final HLB of 10 or more.

Examples of suitable surfactants include, but are not limited to, polyoxyethylene derivatives of natural or hydrogenated vegetable oils such as castor oil; polyoxyethylene-sorbitan esters of fatty acids, such as mono-, di- and tri-lauryl, palmityl, stearyl and oleyl; polyoxyethylene fatty acid esters; polyoxyethylene-polyoxypropylene copolymers; alkyl/dialkylsulfate, sulfonate or sulfosuccinate salt; sodium lauryl sulfate; phospholipids such as lecithins; trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols; sorbitan fatty acid esters; pentaerythritol fatty acid esters and polyalkylene glycol ethers; and the like. The surfactants may be used alone or in combination.

Although any pharmaceutically acceptable surfactant may be used in the binary system of the invention, certain surfactants are preferred. These include polyoxyethylene castor oil derivatives, such as polyoxyethylene-glycerol-triricinoleate, also known as polyoxyl 35 castor oil (CREMOPHOR® EL), or polyoxyl 40 hydrogenated castor oil (CREMOPHOR® RH40, both available from BASF Corp.); mono-fatty acid esters of polyoxyethylene (20) sorbitan, such as polyoxyethylene(20)sorbitan monooleate (TWEEN® 80, available), polyoxyethylene monostearate (TWEEN® 60), polyoxyethylene (20) sorbitan monopalmitate (TWEEN® 40), polyoxyethylene (20) sorbitan monolaurate (TWEEN® 20, all available from ICI Surfactants, Wilmington, Delaware); polyglyceryl esters, such as polyglyceryl oleate; and LABRAFIL® M1944 CS polyoxyethylated kernel oil (available from Gattefossé Corporation).

Of the above, the polyoxyethylene castor oil derivatives are particularly preferred, with CREMOPHOR® EL and CREMOPHOR® RH40 the most preferred. As the proportion of this type of surfactant in the compositions of the invention increases above about 10% by weight, and upon dilution of the formulation with water or juice, the particle size of the resulting microemulsion or micellar solution decreases. For example, at a surfactant concentration of about 10% by weight, the particle size of the diluted formulation is generally less than about 120 nm; at a concentration of about 30% by weight the particle size is generally less than about 100 nm; and at a concentration of about 50% by weight the particle size is generally less than about 50 nm.

The surfactant component generally comprises about 5 to 90% by weight of the composition. Preferably the surfactant comprises about 10 to 60% by weight of the composition, and more preferably about 30 to 50% by weight.

The active ingredient, for example, a cyclosporine, will normally be present in amounts ranging from about 0.01 to 50% by weight of the composition. In a preferred embodiment of the invention the active ingredient is present in an amount ranging between about 5 and 15% by weight, with about 10% by weight particularly preferred. Of course, those of skill in the art understand that the amount of active ingredient present in the composition will vary with the particular situation, including the mode of administration, the size and condition of the subject, and other factors.

If desired, the compositions of the invention may additionally comprise other pharmaceutically acceptable excipients such as fillers, diluents, flavoring agents, coloring agents, antioxidants, preservatives such as antibacterial or antifungal agents, and the like. Such additives, if present, may comprise about 0.01 to 10% by weight of the composition.

The pharmaceutical compositions of the invention may be administered by any of the methods known in the art. Such methods include but are not limited to oral administration of a suspension formed by mixing the composition of the invention with an aqueous medium such as water, milk or juice; in the form of a soft elastic or hard gelatin capsule into which the composition of the invention has been directly placed; parenteral administration including intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection or infusion; or topical administration, such as by ointments, drops or transdermal patches. Topical formulations, intended for administration to the skin or mucosa including the surfaces of the lung and eye, may be prepared directly from the compositions of the invention or from a suspension or microsuspension prepared by combining an appropriate composition of the invention with an aqueous diluent. Such topical formulations may include additional excipients as necessary, for example to modify consistency or the rate of absorption of the active ingredient.

In preparing the compositions of the present invention, the above components may be combined in any order with mixing or light agitation to ensure complete solubilization. If necessary, the mixture may be warmed slightly to aid liquification and dissolution. If all components of the formulation are liquid at ambient temperatures (about 25 to 30°C), they may be combined without heating.

The pharmaceutical compositions and formulations of the invention may be administered in a sufficient amount, and for a sufficient time, as required to provide the desired therapeutic effect. The specific therapeutically effective dosage level will be dependent on a number of factors including the specific condition being treated, the severity of the disorder, the activity of the particular active ingredient, the specific formulation employed, the time and method of administration, the duration of treatment, and other factors which are well known in the medical arts.

The invention will be better understood by reference to the following examples, which are understood to be illustrative only and are not intended as a limitation upon the scope of the invention.

Each of the compositions was prepared by placing the component or components of the lipophilic phase into a suitable vessel, heating to a temperature of about 40 to 45°C, and mixing until uniform. The surfactant or surfactants were pre-melted, if necessary, and added, with continuous mixing, while maintaining the temperature at about 40 to 45°C. The active

ingredient(s) were then added, stirring continuously, with the temperature maintained at about 40 to 45°C. The product was transferred to appropriate containers and allowed to cool.

The following table shows the chemical identity of the various products used in the example formulations:

Table 1

| Trade Name | Chemical Designation |
|---|---|
| TWEEN® 80 | Polyoxyethylene (20) sorbitan monooleate |
| MIGLYOL® 812 | Caprylic/capric triglyceride |
| CREMOPHOR® EL | Polyoxyl 35 castor oil |
| CREMOPHOR® RH40 | Polyoxyl 40 hydrogenated castor oil |
| CAPMUL® MCM | Mono- and diglyceryl caprylate/caprate |
| GELUCIRE® 33/01 | $C_8/C_{18}$ triglycerides from hydrogenated palm oil |
| MAISINE® | Transesterified mono-, di- and triglycerides from corn oil |
| CAPMUL® GMO | Glyceryl oleate (mono-, di- and triesters) |
| POLOXAMER® 237 | Polyoxypropylene/polyoxyethylene block copolymer |
| PECEOL® | Glyceryl oleate (mono-, di- and triesters) |
| PLURONIC® F68 | Polyoxypropylene/polyoxyethylene block copolymer |
| CAPROL® 10G4O | Decaglycerol tetraoleate |
| MYVEROL® 18-99 | Distilled monooleate from rapeseed oil |
| SPAN® 80 | Sorbitan monooleate |

Using the above procedures and excipients, Examples 1 to 27 were prepared to illustrate the binary compositions of the present invention. Example 28 was prepared as a comparative example of a formulation comprising a lipophilic solvent in the absence of a surfactant.

Example 1

| Component | %w/v |
|---|---|
| Cyclosporin A | 10 |
| TWEEN® 80 | 25 |
| MIGLYOL® 812 | qs 100 ml |

Example 2

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 20 |
| Sesame oil | 70 |

Example 3

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® RH40 | 5 |
| CAPMUL® MCM | 85 |

Example 4

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® RH40 | 15 |
| CAPMUL® MCM | 75 |

Example 5

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® RH40 | 10 |
| CAPMUL® MCM | 80 |

Example 6

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® RH40 | 25 |
| CAPMUL® MCM | 65 |

Example 7

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 40 |
| MIGLYOL® 812 | 40 |
| Hydrogenated Vegetable Oil | 2 |
| GELUCIRE® 33/01 | 8 |

Example 8

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 45 |
| MIGLYOL® 812 | 45 |

Example 9

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 10 |
| MAISINE® | 80 |

Example 10

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 25 |
| MAISINE® | 65 |

Example 11

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 25 |
| CAPMUL® GMO | 65 |

Example 12

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| POLOXAMER® 237 | 5 |
| CAPMUL® MCM | 85 |

Example 13

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 5 |
| PECEOL® | 85 |

Example 14

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 10 |
| PECEOL® | 80 |

Example 15

| Component | %w/v |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 30 |
| CAPMUL® MCM | 15 |
| MIGLYOL® 812 | qs 100 ml |

Example 16

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 15 |
| PECEOL® | 75 |

Example 17

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 25 |
| PECEOL® | 65 |

Example 18

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® RH40 | 45 |
| CAPMUL® MCM | 45 |

Example 19

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| PLURONIC® F68 | 10 |
| CAPMUL® GMO | 80 |

Example 20

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| PLURONIC® F68 | 5 |
| CREMOPHOR® EL | 10 |
| CAPMUL® GMO | 75 |

Example 21

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 40 |
| Propylene glycol laurate | 50 |

Example 22

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 30 |
| MYVEROL® 18-99 | 60 |

Example 23

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 20 |
| MYVEROL® 18-99 | 30 |
| Propylene glycol laurate | 40 |

Example 24

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 30 |
| Propylene glycol laurate | 60 |

Example 25

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 5 |
| SPAN® 80 | 15 |
| MYVEROL® 18-99 | 70 |

Example 26

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 35 |
| Oleic acid | 15 |
| MYVEROL® 18-99 | 40 |

Example 27

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CREMOPHOR® EL | 30 |
| CAPROL® 10G4O | 30 |
| MYVEROL® 18-99 | 30 |

Example 28

| Component | %w/w |
|---|---|
| Cyclosporin A | 10 |
| CAPMUL® MCM | 90 |

The oral bioavailability of the compositions of the present invention was evaluated in fasted beagle dogs as follows:

The compositions of Examples 1 to 19 and control samples consisting of the commercial cyclosporine products SANDIMMUNE® SEC (soft elastic capsule) and OPTORAL® SEC were filled into hard and soft gelatin capsules in quantities which, when delivered to the subjects, delivered 50 mg/kg of cyclosporine to each dog. Blood concentration data was normalized to a 5 mg/kg dose in each dog. The soft elastic capsules were heat-sealed and all capsules were inspected to confirm the absence of leakage.

Six dogs were fasted and then at time t=0 were given one of the encapsulated compositions. Blood samples were taken at 15, 30, 60 and 90 minutes and at 2, 4, 6, 9, 12, 15 and 24 hours after dosing and analyzed for the blood concentration of cyclosporine. From this data the maximum blood serum concentration ($C_{max}$), time from dosing until maximum blood serum concentration ($T_{max}$) and total presence (area under curve, or AUC) as well as the respective standard deviations were computed and are shown below in Table 2:

Table 2

Blood Concentrations of Cyclosporine

After 5 mg/kg Oral Dosing of Dogs

| Example Number | $C_{max}$ (ng/ml) | $T_{max}$ (hours) | AUC (ng·hour/ml) |
|---|---|---|---|
| 1 | 629.8 ± 205.9 | 1.3 ± 0.4 | 3548.8 ± 1152.1 |
| 2 | 814.6 ± 156.5 | 1.3 ± 0.5 | 5519.2 ± 1181.6 |
| 3 | 472.7 ± 246.8 | 1.3 ± 0.4 | 2781.6 ± 1292.6 |
| 4 | 857.9 ± 357.7 | 1.3 ± 0.5 | 4879.3 ± 2274.0 |
| 5 | 866.3 ± 316.4 | 1.4 ± 0.4 | 4672.1 ± 1847.8 |
| 6 | 852.4 ± 454.2 | 1.8 ± 1.2 | 4664.8 ± 1555.9 |
| 7 | 1001.1 ± 264.2 | 1.7 ± 0.3 | 5974.7 ± 1729.3 |
| 8 | 1208.2 ± 335.3 | 1.4 ± 0.4 | 6495.6 ± 1452.0 |
| 9 | 1139.2 ± 400.1 | 1.1 ± 0.2 | 6824.5 ± 3392.2 |
| 10 | 945.1 ± 122.9 | 1.3 ± 0.3 | 5113.2 ± 1340.6 |
| 11 | 1132.0 ± 126.5 | 1.2 ± 0.3 | 6151.5 ± 1828.5 |
| 12 | 412.4 ± 183.9 | 2.4 ± 1.3 | 3233.2 ± 1690.6 |
| 13 | 733.2 ± 159.0 | 1.5 ± 0.5 | 4117.7 ± 1300.6 |
| 14 | 680.7 ± 110.9 | 1.2 ± 0.3 | 3731.4 ± 751.3 |
| 15 | 634.3 ± 453.3 | 0.9 ± 0.2 | 3369.8 ± 2682.3 |
| 16 | 971.7 ± 383.1 | 1.5 ± 0.5 | 5000.3 ± 1368.9 |
| 17 | 1078.2 ± 409.6 | 1.2 ± 0.3 | 5724.6 ± 1389.5 |
| 18 | 872.2 ± 226.8 | 1.5 ± 0.5 | 5551.6 ± 2243.9 |
| 19 | 819.3 ± 345.9 | -- | 4718.3 ± 1850.5 |
| 20 | 798.4 ± 177.8 | -- | 4627.7 ± 1028.1 |
| 21 | 993.7 ± 250.6 | -- | 6055.2 ± 1159.2 |
| 22 | 973.0 ± 238.0 | -- | 5539.7 ± 2569.7 |
| 23 | 946.9 ± 69.4 | -- | 5175.0 ± 936.6 |
| 24 | 1002.2 ± 181.5 | -- | 5580.9 ± 2165.2 |
| 25 | 663.2 ± 108.0 | -- | 4557.4 ± 640.0 |
| 26 | 962.0 ± 149.3 | -- | 5821.3 ± 397.9 |
| 27 | 871.2 ± 275.4 | -- | 6730.5 ± 2708.6 |
| 28 | 448.8 ± 199.2 | 1.5 ± 0.3 | 2547.2 ± 1027.8 |

For SANDIMMUNE® SEC the $C_{max}$ was 947.9 ± 295.1 ng/ml and the AUC was 4837.7 ± 1215.1 ng·hour/ml. For OPTORAL® SEC the $C_{max}$ was 1196.6 ± 348.3 ng/ml and the AUC was 6049.1 ± 971.1 ng·hour/ml.

The foregoing detailed description and examples are merely illustrative and are not to be construed as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. It is expected that various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and may be made without departing from the spirit and scope of the invention.

What is claimed is:

1. A binary pharmaceutical composition comprising:
   (a) a cyclosporine;
   (b) a lipophilic phase; and
   (c) a surfactant.

2. A binary composition according to Claim 1 wherein the cyclosporine comprises cyclosporin A.

3. A binary composition according to Claim 1 wherein (b) comprises a lipophilic component selected from the group consisting of a propylene glycol mono- and/or di-caprylate/caprate; a propylene glycol mono- and/or dilaurate; vegetable oil; corn oil; sesame oil; safflower oil; peanut oil; olive oil; cottonseed oil; glyceryl monostearate; glyceryl caprylate/caprate; glyceryl mono-, di- and/or trioleate; caprylic/capric triglyceride; a fractionated coconut oil; and mixtures thereof.

4. A binary composition according to Claim 1 wherein (b) comprises a fatty acid triglyceride.

5. A binary composition according to Claim 1 wherein (b) is caprylic/capric triglyceride.

6. A binary composition according to Claim 1 wherein (b) comprises glyceryl mono- or dicaprylate/caprate; glyceryl oleate; propylene glycol laurate; or a mixture thereof.

7. A binary composition according to Claim 1 wherein (c) comprises a nonionic surfactant.

8. A binary composition according to Claim 1 wherein (c) comprises a polyoxyethylene derivative of a natural or hydrogenated vegetable oil; a polyoxyethylene-sorbitan-fatty acid ester; a polyoxyethylene fatty acid ester; a saturated polyglycol glyceride; a sorbitan fatty acid ester; or a mixture thereof.

9. A binary composition according to Claim 1 wherein (c) comprises a polyoxyethylene glycolated natural or hydrogenated vegetable oil.

10. A binary composition according to Claim 1 comprising:
    (a) between 0.03% and 25% by weight cyclosporine;
    (b) between 10% and 90% by weight lipophilic phase; and
    (c) between 5% and 90% by weight surfactant.

11. A binary composition according to Claim 1 comprising:
    (a) between 5% and 15% by weight cyclosporine;
    (b) between 20% and 85% by weight lipophilic phase; and
    (c) between 10% and 60% by weight surfactant.

12. A binary composition according to Claim 1 comprising:
    (a) 10% by weight cyclosporine;
    (b) between 40% and 60% by weight lipophilic phase; and
    (c) between 30% and 50% by weight surfactant.

13. A binary pharmaceutical composition comprising:
    (a) cyclosporin A;
    (b) propylene glycol laurate; and
    (c) polyoxyl 35 castor oil.

16. A binary composition according to Claim 13 wherein (a), (b) and (c) are present in a ratio of approximately 10:50:40 by weight.

# INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 98/04899

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/107 A61K9/48 A61K38/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | GB 2 228 198 A (SANDOZ LTD) 22 August 1990<br>see page 29 - page 30; examples 1,2 | 1-12,16 |
| X | EP 0 760 237 A (CIPLA LIMITED) 5 March 1997<br>see page 2, line 47 - line 57<br>see page 4, line 23 - page 5, line 42 | 1-4,<br>7-12,16 |
| X | WO 96 33697 A (YISSUM RES DEV CO ;BENITA SIMON (IL); KLEINSTERN JACKIE (IL); GERS)<br>31 October 1996<br>see page 19; table VIII<br>see page 9, line 6 - line 29 | 1,2,7,8,<br>10,11 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 August 1998 | 26/08/1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Boulois, D |



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# INTERNATIONAL SEARCH REPORT

Information on patent family members

In: ational Application No
PCT/US 98/04899

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| GB 2228198 A | 22-08-1990 | BE 1005236 A | 08-06-1993 |
| | | CH 680650 A | 15-10-1992 |
| | | CY 1886 A | 05-04-1996 |
| | | DE 4005190 A | 23-08-1990 |
| | | FR 2643262 A | 24-08-1990 |
| | | HK 149595 A | 29-09-1995 |
| | | IT 1240765 B | 17-12-1993 |
| | | JP 1888154 C | 07-12-1994 |
| | | JP 2255623 A | 16-10-1990 |
| | | JP 6011703 B | 16-02-1994 |
| | | US 5639724 A | 17-06-1997 |
| | | US 5759997 A | 02-06-1998 |
| | | US 5652212 A | 29-07-1997 |
| EP 0760237 A | 05-03-1997 | AU 6216296 A | 06-03-1997 |
| WO 9633697 A | 31-10-1996 | AU 692255 B | 04-06-1998 |
| | | AU 2449195 A | 18-11-1996 |